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The Complex Relationship between Weather and Dengue Virus Transmission in Thailand

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Abstract. Using a novel analytical approach, weather dynamics and seasonal dengue virus transmission cycles were profiled for each Thailand province, 1983–2001, using monthly assessments of cases, temperature, humidity, and rainfall. We observed systematic differences in the structure of seasonal transmission cycles of different magnitude, the role of weather in regulating seasonal cycles, necessary versus optimal transmission “weather-space,” basis of large epidemics, and predictive indicators that estimate risk. Larger epidemics begin earlier, develop faster, and are predicted at *Onset change-point* when case counts are low. Temperature defines a viable range for transmission; humidity amplifies the potential within that range. This duality is central to transmission. Eighty percent of 1.2 million severe dengue cases occurred when mean temperature was 27–29.5°C and mean humidity was > 75%. Interventions are most effective when applied early. Most cases occur near *Peak*, yet small reductions at *Onset* can substantially reduce epidemic magnitude. Monitoring the *Quiet-Phase* is fundamental in effectively targeting interventions pre-emptively.

INTRODUCTION

Dengue viruses cause more human morbidity and mortality than any other arthropod-borne virus. Dengue fever and the more severe dengue hemorrhagic fever (DHF) represent a formidable and growing health burden, causing an estimated 390 million infections and 500,000 hospitalizations annually.^{1,2} Vaccine research is ongoing, thus control efforts currently focus on the principal mosquito vector, *Aedes aegypti*, with limited resources and often limited success. Innovative research in dengue surveillance and prevention aims to integrate emerging technologies into an effective multi-tiered approach for disease reduction.^{3,4} Dynamic estimations of risk are needed to guide the development of more effective surveillance-intervention strategies and use of prevention resources, especially for resource-limited, endemic countries that suffer recurrent epidemics with severe disease. A fundamental roadblock to effective use of intervention resources is limited understanding of the relationship between the environment and transmission dynamics of the four dengue virus (DENV) serotypes. Understanding the role of the environment can potentially guide estimates of the timing, location, and magnitude of risk and thus inform effective use of resources.

Thailand experiences hyper-endemic DENV transmission, with seasonal cycles of severe disease that erratically vary in magnitude across provinces and from year to year.^{5–7} Extreme spatial and temporal variance makes dengue prediction and prevention a constantly moving target. A central complexity in anticipating epidemics is the interaction between transmission-regulating factors that are specific to mosquitoes and those specific to humans.^{8–16} We developed an epidemic assessment tool for examining the structure of seasonal transmission cycles over two decades across Thai provinces. We applied this tool to investigate the role of weather in regulating the timing and magnitude of dengue epidemics and the interaction between weather-based and non-weather-based regulation of transmission.

We explore virus transmission in terms of a single reproduction of infection, i.e., transmission from one infected human to a mosquito, which later becomes infective and transmits the virus to a second human (Figure 1). The likelihood of a single reproduction of infection in a specific location and time reflects a combination of probabilities associated with different processes and events. For example, local human-vector contact dynamics reflect abundance of adult female vectors, frequency of biting, mosquito host preference, size of a vector's movement space (typically the span of 2–3 houses) and number of humans that are likely to enter that space at particular time points.^{17–23} The potential for a vector to become infective is limited by length of the extrinsic incubation period (EIP) and probability of the vector surviving the EIP.^{10,17,21,24} Even when abundance, probability of vector-human contact, and probability of vector survival beyond the EIP are high, if post-EIP contact is with a human already immune to the infecting serotype, no reproduction of infection will occur. Conversely, if the affected humans are susceptible to circulating serotypes, but mean vector survival is shorter than EIP, the probability of producing a new human infection will be low. When a strategic combination of increased probabilities of critical events exist in the same space *and* time across many “connected” localities, conditions are suitable for many human infections to occur; i.e., an epidemic.

Field and laboratory studies have revealed relationships between weather and specific aspects of the vector life cycle, vector behavior, and reproduction of the pathogen in the vector. A transition in length of EIP between temperatures of 26 and 30°C with accelerated EIP shortening above 30°C was shown in laboratory tests.^{24,25} Larval development was negatively affected by extreme high or low temperatures.^{17,21,26–31} Delay in first blood meal, length of the gonotrophic cycle, and rates of multiple blood feeding per egg laying cycle were associated with temperature.^{17,21,23,26,28,32–34} Temperature, but not rainfall, was correlated with adult female mosquito abundance in Thailand.²² Adult mosquito survival rates were linked with lower temperature and higher humidity.^{17,21} Vector competence varied with mean temperature and diurnal temperature range and increased in moderate temperatures combined with high humidity.^{25,35} We expect that these complex relationships motivate weather-induced seasonal changes in the probabilities of specific transmission-critical events and thus regulate

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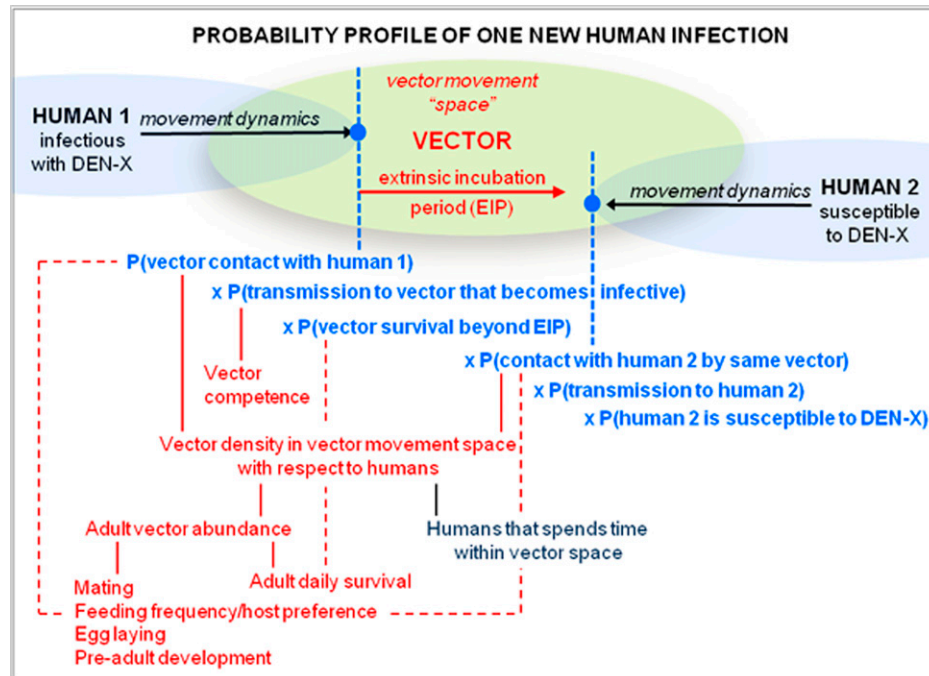


FIGURE 1. Probability profile view for transmission of dengue virus. Diagram depicts multiple stochastic processes (associated with humans and mosquitoes), which interact to formulate an overall probability of a single human-vector-human transmission of dengue virus.

observed seasonal transmission cycles in dengue-endemic areas. We investigated whether there is evidence that these biological links to the environment manifest as systematic and predictable epidemic regulation and explored how this regulation is expressed with respect to the structure of seasonal cycles in dengue disease.

Seasonal cycles of dengue disease are observed in every Thai province. Weather patterns vary geographically providing a broad range of conditions for potential virus transmission. Annual monthly temperature ranges 10–42°C and varies north to south. In February–May temperatures rise and

humidity is lowest. The rainy season (May–October and later on the southern-east coast) brings rising humidity and gently falling temperatures. Temperatures drop in winter (October–February) particularly in northern Thailand, whereas the south remains mild year round. Annual rainfall is 1–2 m or more throughout. Northern winters are mostly dry. Figure 2 illustrates the space-time variation in DHF cases and weather patterns of three geographically distinct provinces: Udon Thani (northeast), Bangkok (central), and Trang (south). Of particular importance with respect to DENV transmission is the phase difference between annual temperature and humidity cycles, the contrast in annual temperature and humidity ranges from north to south and geographic variations in the timing of the rainy season.

We applied empirical disease and weather data spanning 72 provinces and 228 months (1983–2001) to examine how combined influences of weather on different mosquito dynamics are expressed in endemic virus transmission in Thailand. We developed a diagnostic tool for comparatively assessing seasonal DENV transmission dynamics across 1,368 province-years and investigated the following questions: 1) Are there systematic differences between the structure of seasonal transmission cycles of different magnitude? 2) What is the role of weather in the structure of seasonal cycles? 3) Is there a necessary versus optimal transmission “weather-space” for supporting epidemics of varying magnitude? 4) Do year-to-year weather fluctuations provide the basis for large epidemics? 5) What predictive indicators could effectively guide a dynamic assessment of risk and help target interventions pre-emptively?

MATERIALS AND METHODS

The DHF cases by province-month for 1983–2001 provided by the Thailand Ministry of Public Health were used as a

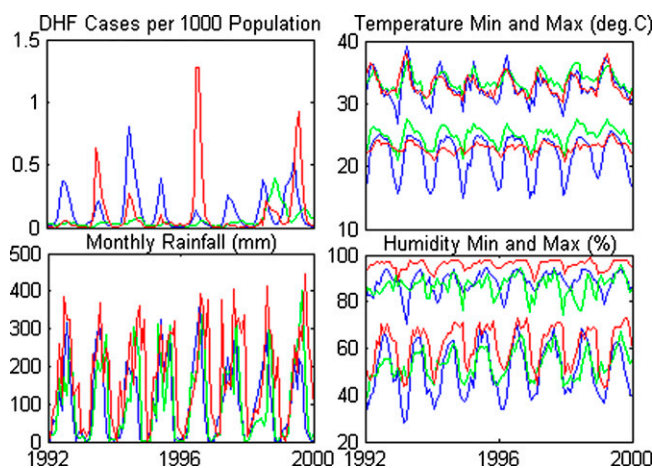


FIGURE 2. Geographic and temporal variation in dengue virus transmission and weather in Thailand. Patterns of weather (temperature, humidity, and rainfall) and monthly dengue hemorrhagic fever (DHF) incidence rates are shown for three Thai provinces, 1992–2000: blue, Udon Thani (northeast); green, Bangkok (south-central); and red, Trang (south).

surrogate for the space-time pattern of all human DENV infections. We expect DHF cases to be the most consistently reported dengue cases in Thailand and reflect relative changes in dengue disease in the local population. Population data from the Thailand National Statistics Office were used to assess incidence rates. Weather data (temperature, humidity, and rainfall) by province-month were developed from daily records of 84 principal and 996 secondary weather stations in Thailand.^{36–38} Monthly maximum (max), minimum (min), and mean values for temperature and humidity represent means of daily values. A spatial 1 km grid of Thailand was generated for each weather component by month, using Delaunay triangulation of weather stations nearest each grid point, from which province-month observations were derived by averaging over grid points that fall within a province.

Epidemic assessment tool. We developed an epidemic assessment tool (Figure 3) to facilitate a structured comparison of DENV transmission and weather conditions across a large number of seasonal cycles. A seasonal cycle of dengue transmission per province was evidenced by reported DHF cases, thus 1,368 seasonal cycles (72 provinces \times 19 years) were examined. Each cycle was partitioned into four distinct functional phases defined by four key change-points in transmission dynamics: 1) *Quiet Phase*—a period of minimal cases; 2) *Development Phase*—characterized by accelerating DHF case counts likely associated with effective reproductive rate $R(t) > 1$; 3) *Peak Plateau Phase*—characterized by DHF case counts near the seasonal peak level and likely associated with

$R(t)$ hovering close to 1; and 4) *Decline Phase*—characterized by declining DHF case counts likely associated with $R(t) < 1$.³⁹

Four change-points, labeled *Nadir*, *Onset*, *Peak*, and *Decline*, identify the time points within each cycle in which key transitions in seasonal transmission dynamics occur and define the four functional phases described previously (see Figure 3). Change-points were identified within each transmission cycle using statistical algorithms applied to the 1983–2001 monthly time series of reported DHF cases for each province. *Peak* was defined as the month of maximum cases during each cycle. It represents the time when potential epidemic development ends and $R(t)$ is no longer > 1 . *Nadir* was defined as the month of lowest case count between two consecutive *Peak* markers, not confined to the same calendar year. Lowest case count often occurred in multiple months, thus we tracked the first and last occurrence of *Nadir* per cycle. (Last *Nadir* is referenced in results of analyses.) *Onset* was defined as the first month following *Nadir* in which evidence of potential epidemic development was observed. We assumed a Poisson flow of cases during the period of lowest virus transmission applying a Poisson distribution based on the mean of monthly case counts from the month preceding first *Nadir* to the month following last *Nadir*. This Poisson distribution reflects current local conditions of transmission during the quiet time of the transient cool dry season. *Onset* occurred in the first month when the province DHF case count indicated the Poisson distribution of the quiet season was no longer valid, defined as exceeding the 99th percentile of the Poisson cumulative distribution function. Thus, *Onset* is based on a relative measure that corresponds to a change defined by the number of cases observed locally during the quiet season, rather than a standardized threshold of cases or a standardized increase in cases. *Onset* represents the time point when potential epidemic development begins. Similarly, *Decline* is the first month in which evidence of a significant drop in number of cases from *Peak* is observed. A Poisson distribution based on number of cases at *Peak* describes the local flow of cases during conditions at *Peak*. The *Decline* marker is defined as the first month in which the number of cases falls below the 1st percentile of the Poisson cumulative distribution function defined at *Peak*. (See Methods in the Supplemental Information for further details regarding change-points.)

The four change-points detailed previously define the four functional phases within each seasonal cycle (Figure 3). The period from first occurrence of *Nadir* to *Onset* represents the *Quiet Phase* when transmission is low and epidemic development is not observed. *Onset* to *Peak* is the *Development Phase* associated with $R(t) > 1$. *Peak* to *Decline* is the *Peak Plateau Phase* when $R(t)$ is likely close to one and case counts remain similar to *Peak* level as defined by the Poisson distribution at *Peak*. From *Decline* to first occurrence of *Nadir* is the *Decline Phase* when $R(t) < 1$ and case counts are falling. This diagnostic structure was defined for each of 1,368 seasonal cycles to facilitate a structured comparison of transmission and weather dynamics across seasonal incidence profiles of varying magnitude and different geographic zones. In pre-analysis, 9.5% of cycles were excluded from further consideration because it was not possible to identify this diagnostic structure. The excluded group consisted of very low incidence province-years in which *Peak* or *Onset* change-points could not be defined.

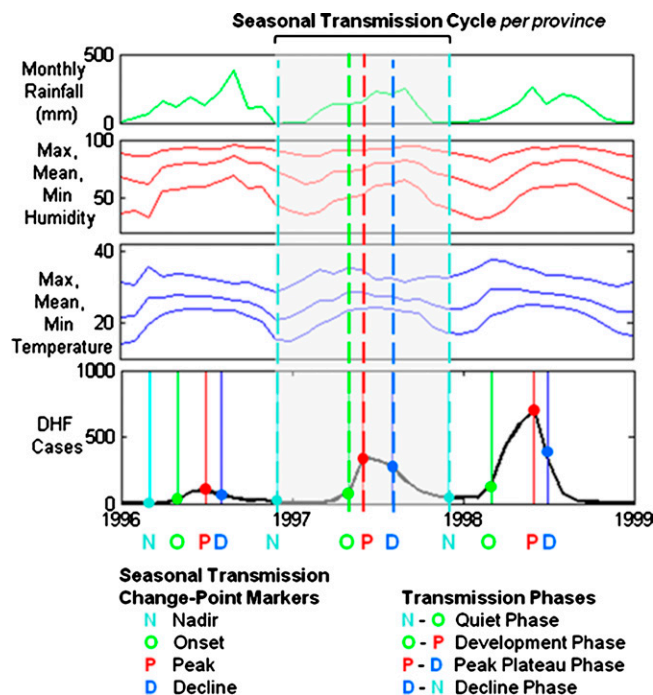


FIGURE 3. Epidemic assessment tool applied to 1,368 seasonal transmission cycles in Thailand. The diagnostic tool defines four seasonal change points in the dynamics of transmission and thus four transmission phases in each seasonal dengue transmission cycle per province. This structure is used to examine the relationship between weather dynamics and dengue virus transmission dynamics at each transmission change point for seasonal cycles of varying incidence magnitude. The tool was applied to 72 provinces over 19 years, thus allowing examination of 1,368 seasonal transmission cycles.

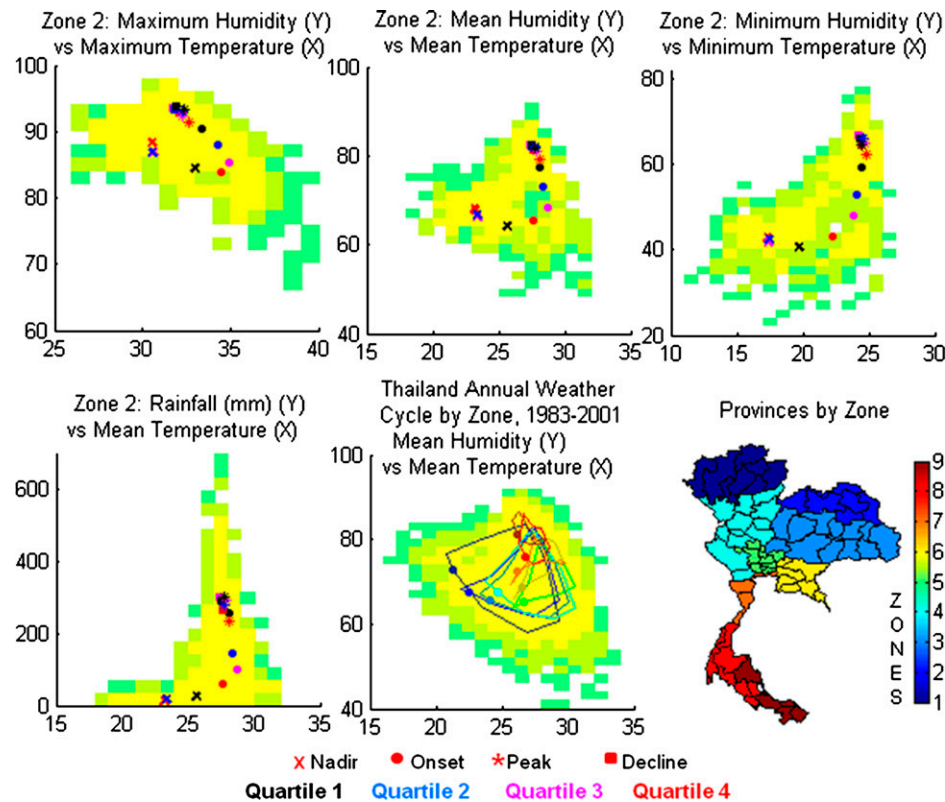


FIGURE 4. Range of weather conditions and timing of change-points by incidence quartile in Thailand weather-space. In top row and bottom left panel, weather range for zone 2 is shown in yellow - light green - dark green background. Light green indicates weather conditions that occur in < 0.05% of province-months in zone 2 throughout the 19-year period. Dark green indicates weather occurring in < 0.01% of province-months for zone 2. Mean timing of zone 2 change-point markers per incidence quartile is shown in each weather space: Nadir, Onset, Peak, Decline. Incidence quartile associated with each marker is designated by color: red = Q4; magenta = Q3; blue = Q2; black = Q1. In bottom center panel, mean humidity versus mean temperature range is shown for all Thailand as a background for mean monthly weather trajectory shown for nine zones, beginning at the dot in January and moving in a counter-clockwise rotation. Light green indicates weather conditions occurring in < 0.1% of province months in Thailand throughout the 19-year period. Dark green indicates weather occurring in < 0.05% of province months. Bottom right panel indicates assignment of provinces to geographic zones based on correlated weather patterns. Grid interval is 1°C for temperature, 2% for humidity, 30 mm for rainfall.

Seasonal transmission cycles ranged from small outbreaks to large epidemics. The 1,368 seasonal cycles were classified into four incidence rate quartiles with respect to the total pool of incidence rates per seasonal cycle for this time period, Q1 representing the smallest 25% in seasonal incidence rate and Q4 representing the largest 25%. Incidence rate quartiles were: Q1: 0–33.4, Q2: 33.4–73.1, Q3: 73.1–149.0, Q4: 149.0–697.3 DHF cases per 100,000 population. All geographic zones experienced all quartile classes. All provinces experienced all classes except Mae Hong Son and Satun had no class Q4 cycles, Trang had no Q2, and Phra Nakhon Si Ayutthaya and Ratchaburi had no Q1. Provinces were grouped according to nine geographical zones based on weather dynamics to aid with interpretation of results (Figure 4). Zones reflect groups of contiguous provinces with the highest synchronization in temperature cycles and humidity cycles and most similar temperature and humidity ranges. (See Methods in the Supplemental Information for additional description of data preparation and statistical analyses.)

Our investigation focused on relationships between weather dynamics and DENV transmission dynamics across incidence quartiles Q1 to Q4 within a province. We compared timing, DHF incidence rates, and weather conditions at seasonal change-points between incidence quartiles within each

province and compared observed patterns across geographic zones characterized by different weather patterns.

RESULTS

Structure of seasonal DENV transmission cycles. We observed unexpected and significant patterns in comparing seasonal cycles across incidence quartiles within a province and across geographic zones. The timing of seasonal change-points Nadir, Onset, Peak, and Decline (see Methods section for definition of change-points) progressed systematically with respect to incidence quartiles Q1–Q4 within a province (Table 1). Onset occurred earlier in Q4 than Q3 cycles ($P < 0.00001$), earlier in Q3 than Q2 cycles ($P < 0.00001$), and earlier in Q2 than Q1 cycles ($P < 0.00001$) by an average of 0.9, 0.5, and 0.8 months, respectively. In contrast, no significant difference was found in the timing of Peak except Q4 cycles reached Peak earlier than Q3 by 0.24 month on average ($P = 0.0096$). Seasonal timing of all four change-points varied geographically (Figure 5). Onset, Peak, and Decline occur earliest in the northeast and follow in a southwesterly direction, occurring last in south central Thailand (near Bangkok) and the southern peninsula. Time lag in transmission cycles

TABLE 1
Epidemic development parameters at seasonal transmission change-point markers are compared between incidence quartiles

Comparison		Q2-Q1		Q3-Q2		Q4-Q3	
		Mean difference	P value	Mean difference	P value	Mean difference	P value
Timing of marker (month)	nadir	-0.58	0.0001*	-0.19	0.1241	-0.66	< 0.00001*
	onset	-0.79	< 0.00001*	-0.48	< 0.00001*	-0.86	< 0.00001*
	peak	0.17	0.2009	-0.06	0.569	-0.24	0.0096*
Duration (months)	onset to peak	0.96	< 0.00001*	0.42	0.0015*	0.62	< 0.00001*
	onset to decline	0.82	< 0.00001*	0.38	0.0044*	0.41	0.0002*
Development Rate†	onset	0.73	< 0.00001*	0.37	< 0.00001*	0.26	0.0089*
	onset to peak	0.41	< 0.00001*	0.20	0.0037*	0.11	0.0998
DHF cases in marker month	nadir	1.57	0.0065*	7.22	< 0.00001*	6.23	< 0.00001*
	onset	9.97	< 0.00001*	18.41	< 0.00001*	17.06	< 0.00001*
	peak	63.47	< 0.00001*	107.59	< 0.00001*	300.65	< 0.00001*
	decline	39.59	< 0.00001*	70.42	< 0.00001*	196.97	< 0.00001*
Incidence Rate per 100 K Population	nadir	0.23	0.001*	0.57	< 0.00001*	0.99	< 0.00001*
	onset	1.29	< 0.00001*	2.28	< 0.00001*	3.37	< 0.00001*
	peak	7.78	< 0.00001*	14.27	< 0.00001*	41.69	< 0.00001*
	decline	4.47	< 0.00001*	8.72	< 0.00001*	26.56	< 0.00001*

*Significant difference detected when $P \leq 0.0125$. P value is adjusted for group-wise multiple comparisons.

†Development Rate at onset for province p , year y = $\text{DHF Cases}_{p,y,t=\text{onset month}+1} / \text{DHF Cases}_{p,y,t=\text{onset month}}$.
Development Rate for onset to peak is mean DR observed during months of development phase.
DHF = dengue hemorrhagic fever; DR = Development Rate.

from northeastern to southwestern Thailand is as large as 6 months and represents an important factor in regional transmission dynamics. This lag appears to be induced by local weather conditions.

Duration of the Development Phase (Onset to Peak) is longer in Q4 than Q3 cycles ($P < 0.00001$), longer in Q3 than Q2 cycles ($P = 0.0015$), and longer in Q2 than Q1 cycles ($P < 0.00001$) by an average of 0.6, 0.4, and 1 month, respectively.

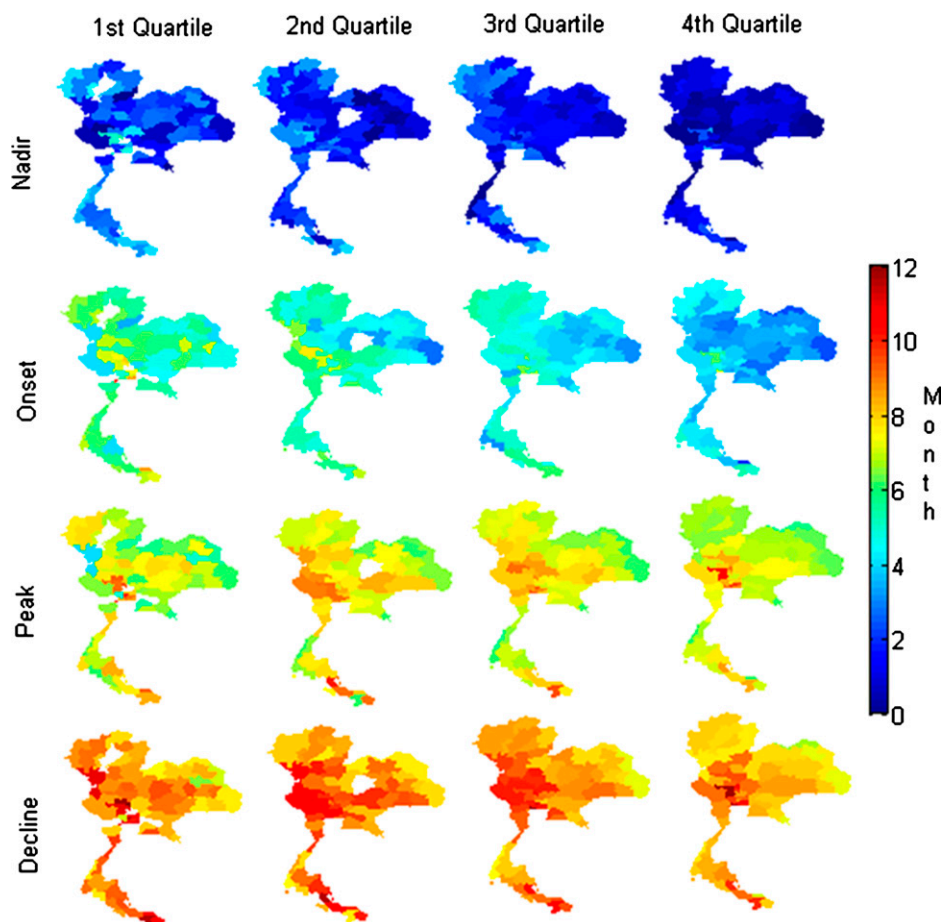


FIGURE 5. Timing of the dengue virus seasonal transmission change-points. Mean month of occurrence of each change-point marker is color-coded by province for each epidemic class (dengue hemorrhagic fever [DHF] incidence quartile). Q1 represents smallest 25% of seasonal transmission cycles in Thailand, 1983–2001. Q4 represents largest 25%.

Tests of duration of Onset to Decline produced similar results (Table 1). Note that the mean difference in duration of the Development Phase across quartiles is similar to the mean shift in timing of Onset across quartiles. Higher incidence transmission seasons begin earlier in general, thereby creating a longer Development Phase. A longer Development Phase by even 2 weeks can significantly increase the size of an epidemic.

Development Rate (DR) per province is higher in higher quartile cycles, particularly at Onset. The DR is the ratio of DHF cases in the current month to DHF cases in the prior month in the same province, or simply the rate in which case counts multiply per month. The DR is related to the effective reproductive rate, $R(t)$, but is a different measure. The $R(t)$ is a dynamic rate derived from all dengue cases, apparent and unapparent, and is difficult to measure. The DR is based on reported DHF cases as a measure of the dynamic rate of change in incidence of severe disease. In Thailand, DR at

Onset is higher in higher quartile transmission seasons (quartile comparisons: Q4:Q3, $P = 0.0089$; Q3:Q2, $P < 0.00001$; Q2:Q1, $P < 0.00001$) with mean differences in DR of 0.26, 0.37, and 0.73 respectively (Table 1). Similar results were observed for DR averaged over the Development Phase. Duration and DR vary geographically, likely from effects of weather on vector dynamics (see maps in Figure 6). Duration of the Development Phase is shorter and DR is higher in northern Thailand where the Development Phase follows cold winters and rapid temperature changes compared with year round mild weather of southern Thailand. This disparity indicates the most effective vector control delivery strategies may vary geographically.

We compared observed cases at the time of each change-point across incidence quartiles per province. As expected, significantly higher case counts are observed in higher quartile cycles at Peak and Decline. More informative and useful for prediction, the same pattern exists at Nadir and

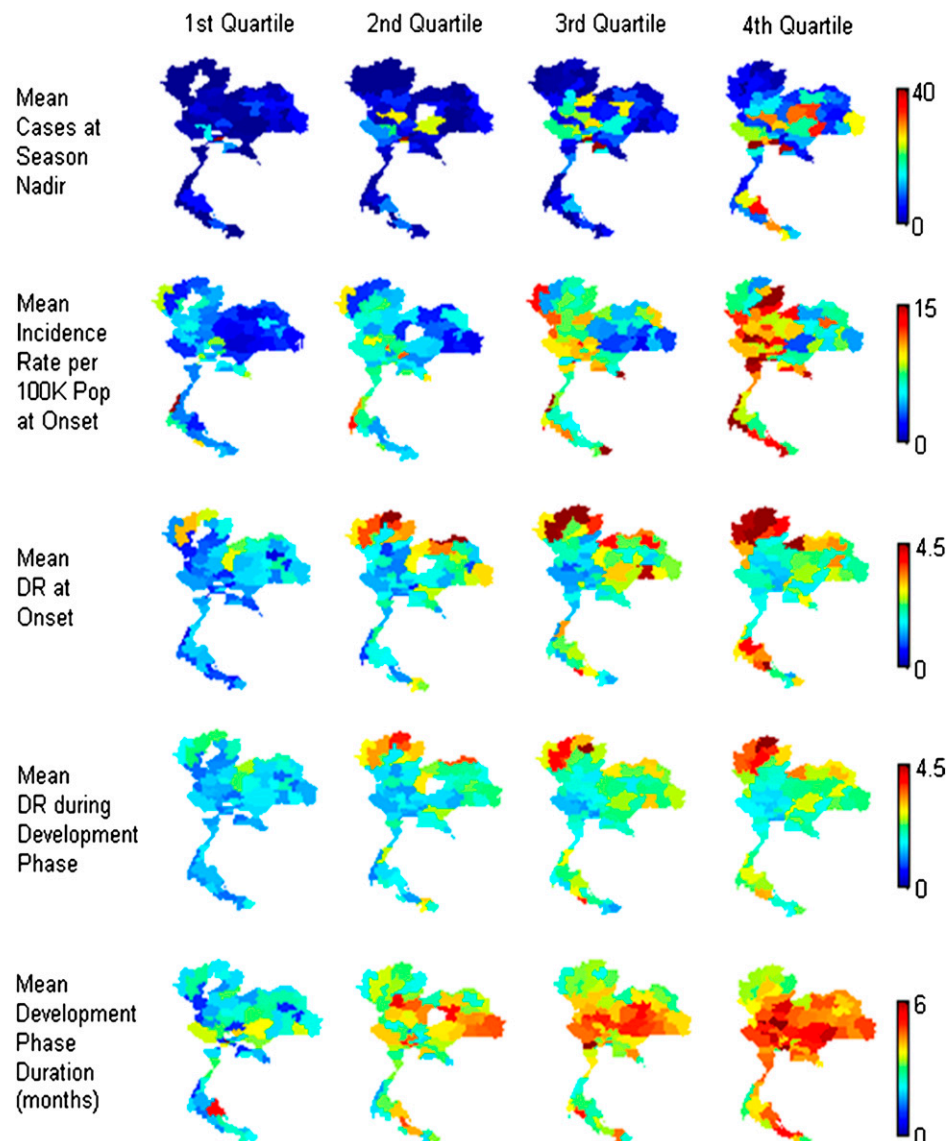


FIGURE 6. Seasonal dengue virus transmission development parameters. Mean observations of epidemic development parameters are color-coded by province for each epidemic class (dengue hemorrhagic fever [DHF] incidence quartile). Q1 represents smallest 25% of seasonal transmission cycles in Thailand, 1983–2001. Q4 represents largest 25%.

Onset: significantly higher case counts are observed in higher quartile cycles at Nadir and Onset. At Nadir, case counts are low, 0–40 in most provinces and frequently < 5 per province. Onset is the first month that evidence of potential epidemic development is detected but case counts are still typically modest. Even with minimal cases, the number of cases at Nadir was significantly higher in higher quartile transmission cycles (quartile comparisons: Q4:Q3, $P < 0.00001$; Q3:Q2, $P < 0.00001$; Q2:Q1, $P = 0.0065$) with mean differences of 6.23, 7.22, and 1.57, respectively. At Onset, case counts and incidence rates were significantly higher in higher quartile cycles (quartile comparisons: Q4:Q3, $P < 0.00001$; Q3:Q2, $P < 0.00001$; Q2:Q1, $P < 0.00001$) with mean differences in incidence rate per 100,000 population of 3.37, 2.28, and 1.29, respectively (Table 1). Thus, epidemic staging occurs early: the dynamics of an epidemic are in place and recognizable by Onset, which is very early in the transmission season and before the steep rise of the epidemic curve associated with epidemic transmission. The geographic distribution of cases at Nadir and Onset by quartile is mapped in Figure 6; northern and northeastern Thailand experience lower incidence rates at Onset than other areas. This is likely influenced by the cold winters of the north and the geographic contrast in local weather conditions during the Quiet Phase. Note that local incidence levels at Onset are typically higher, DR at Onset is higher, and seasonal timing of Onset comes earlier in higher quartile seasonal transmission cycles.

Systematic variation in **a**) cases at Onset, **b**) DR, and **c**) duration of Development Phase plays a central role in the dynamics that determine the incidence quartile of a transmission season. The total number of cases produced during the Development Phase is highly sensitive to very small variations in **a**, **b**, and **c** above. This is shown by a simple hypothetical but realistic example (Equations 1–5). Total cases produced during the Development Phase ($CASES_{DP}$) is the product of cases in one generation of infection at Onset (C_0) multiplied by the effective reproductive rate in each subsequent generation of infection (R_g), for the duration of the Development Phase (G generations):

$$CASES_{DP} = C_0 \times R_{g1} \times R_{g2} \times R_{g3} \times \dots \times R_{gG}, \quad (1)$$

$$CASES_{DP} (C_0 = 10, R_g = 2.0, G = 6) = 1,270 \text{ total cases}, \quad (2)$$

$$CASES_{DP} (C_0 = 10, R_g = 2.0, G = 7) = 2,550 \text{ total cases}, \quad (3)$$

$$CASES_{DP} (C_0 = 13, R_g = 2.0, G = 8) = 6,443 \text{ total cases}, \quad (4)$$

$$CASES_{DP} (C_0 = 18, R_g = 2.4, G = 8) = 33,953 \text{ total cases}, \quad (5)$$

The increase from 1,270 to 33,953 cases during Onset to Peak in a single transmission season (Equations 1–5) results from very small changes in cases at Onset, reproductive rate, and duration of the Development Phase. These hypothetical estimates are consistent with observed ranges in Thailand and the proportional increase in incidence we observed from Q1 to Q2 to Q3 to Q4 seasonal cycles. The structure of Q1–Q4 seasonal transmission cycles described previously indicates that interventions with small but properly targeted effects, such as early small reductions in cases, a slight delay in Onset, or a minimal reduction in $R(t)$ by decreasing adult vector abundance or lifespan can have a substantial impact on the class of a seasonal

transmission cycle. Observed conditions at Onset are predictive. In exploratory studies we found the combination of Onset timing, DR at Onset, and cases at Onset to be highly successful in classifying the outcome of a transmission season.

Relationship between structure of seasonal transmission cycles and weather. Despite a large variance in temperature and humidity ranges across zones, all of Thailand converges to a focal point in the weather-space near 80% mean humidity and 28°C mean temperature in the middle of the rainy season, although all zones do not reach this point at the same time. This point of spatially lagged convergence occurs in a critical area of the weather-space in relation to DENV transmission and has an important impact on space-time dynamics of dengue epidemics in Thailand. The annual weather trajectory in each zone (mapped in Figure 4, bottom center panel) begins in January at low temperature and mid-range humidity and follows a counter-clockwise rotation. The mean path of change-point markers by quartile are shown for zone 2 in Figure 4. Nadir markers occur earliest in the order Q4, Q3, Q2, Q1 followed by Onset markers, in the same quartile order. Peak markers occur highly clustered near the seasonal zenith of humidity, with Q4 often occurring slightly before other quartiles. Decline markers are also clustered and not distant from the Peak cluster in weather-space, occurring just as humidity is decelerating or begins to fall. The weather-space pattern varies across zones; the change-point pattern, however, is similar across zones, even in the limited weather ranges of zones 8 and 9.

Change-points are associated with specific temperature and humidity conditions and timing of the rainy season (Figure 7). We did not observe a strong correlation between seasonal incidence patterns and amount of rainfall; however, it was rare for Onset to occur in any province before the rainy season had begun. Nadir occurs when humidity and temperature are near their lowest point locally. Critical changes occur during the Quiet Phase that stage conditions for Onset. Temperatures rise, the rainy season begins, and maximum temperature approaches its zenith or begins to decline. Commencement of the rainy season and cessation of max temperature rise are associated with the start of humidity rise, which is critical to the Development Phase. By Onset, mean temperature rises to near or above 28°C and then begins a protracted decline, and min temperature rises to near or above 24.5°C. Earliest Onsets locally are associated with higher quartile cycles. Earliest Onsets occur when humidity is low and beginning a precipitous rise. Onset in lower quartile seasons is associated with increasing levels of humidity and Onset in Q1 is associated with conditions near Peak where humidity is approaching its local seasonal high. Large and significant differences in humidity at Onset were observed across quartiles within ranges 84–95.3%, 63.9–83.9%, and 41–67.2% for max, mean, min humidity, respectively (see Tables 2 and 3).

DENV transmission appears to be highly sensitive to specific yet very small changes in weather conditions. The slight but significant difference in timing and weather at Peak in the largest epidemics may define optimum weather requirements for supporting highest levels of transmission in Thailand. During the Development Phase, from Onset to Peak, humidity steeply rises, whereas mean temperature changes minimally in a slow decline. The central tendency of max, mean, and min temperature and humidity at Peak across quartiles is 32.5°C, 28.0°C, 24.5°C, and 92%, 80%, and 63%, respectively. Only

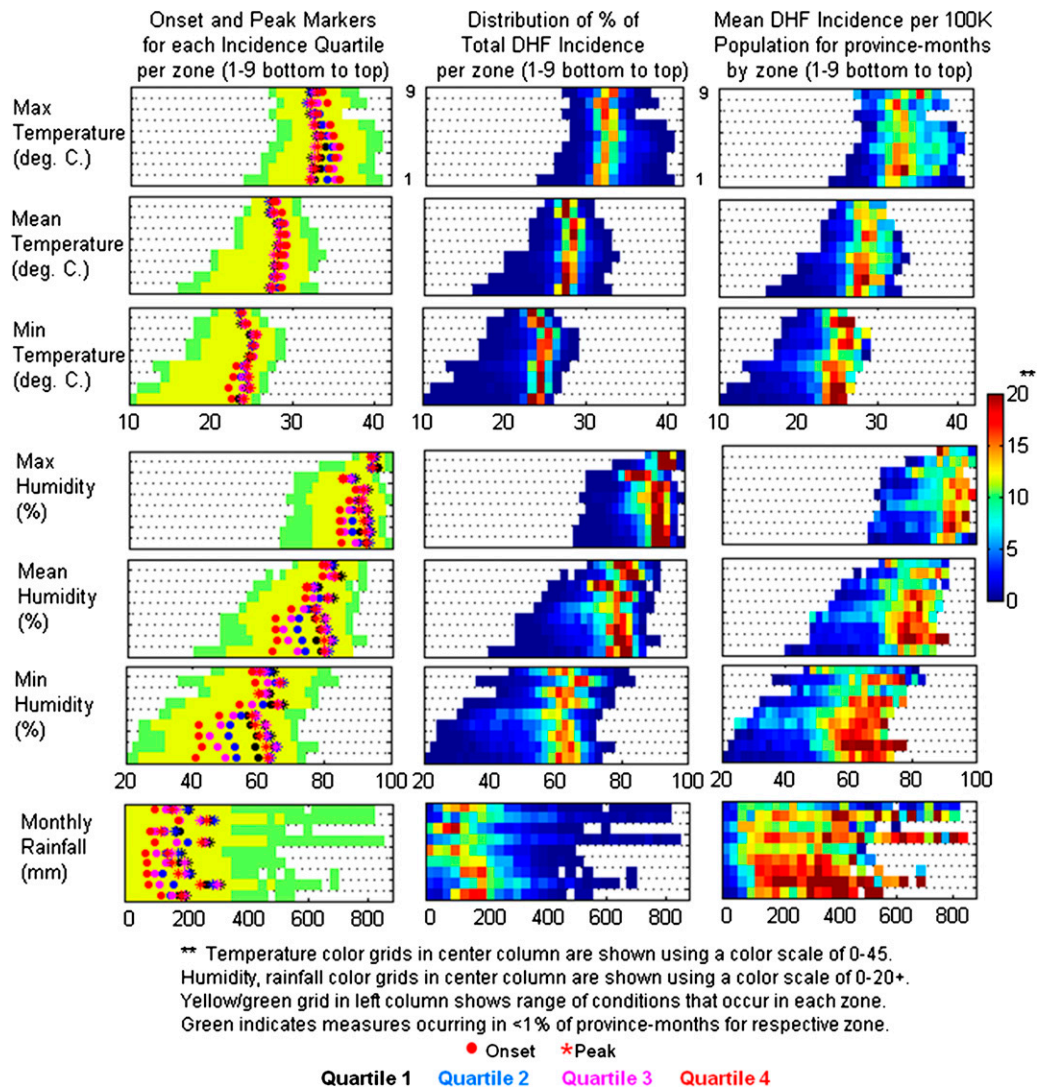


FIGURE 7. Distribution of dengue virus transmission seasonal change-points and dengue hemorrhagic fever (DHF) incidence rates by zone in Thailand. Change-points, Onset, and Peak, by incidence quartile are shown for each weather component in left column. Background indicates weather range for each zone. Within each panel, zones are layered 1–9 bottom to top. (See Figure 4 for spatial designation of zones.) Green background indicates weather occurring in < 1% of province months. Incidence quartile of change-points is designated by color of marker. In center column, DHF incidence rates occurring within the zone are distributed across the weather component range (colors indicate distribution of incidence rates per 100 K population per province-month as percent of sum over weather-space) for each of nine zones. In right column, the mean DHF incidence rate per 100 K population per province-month calculated from all province-months occurring in each weather interval is shown. Note from left column that more extreme weather intervals are rare events in each zone. More extreme weather intervals may be associated with a high incidence but occur rarely and contribute little to the percent of summed incidence rates shown in the center column. Grid interval is 1°C for temperature, 2% for humidity, 30 mm for rainfall.

Q4 weather is significantly different from Q3 at Peak with slightly higher mean temperature (28.1 versus 27.9°C) and lower mean humidity (78.7 versus 79.8%) associated with earlier Q4 Peaks. Decline change-point marks the end of the Peak Plateau Phase and first month of evidence that Decline Phase has begun. Temperature at Decline is slightly, but significantly lower than Peak and humidity is approaching its zenith or just beginning to fall. The central tendency of max, mean, and min temperature and humidity at the Decline change-point is 31.9°C, 27.3°C, 23.8°C, and 92%, 80%, and 63%, respectively. During the Decline Phase, temperature and humidity drop at different rates across zones until the next Nadir.

Transitions occurring from pre-Onset to Onset and from Peak to Decline are pivotal to the regulatory role of weather

in virus transmission. From pre-Onset (2 months before Onset) to Onset significant changes occurred in all weather components and incidence quartiles (see Table 4). From Peak to Decline, a significant drop in temperature for all incidence quartiles and significant rise in humidity only for Q4 were observed. From Onset to Peak, the average change in max, mean, and min temperature was 1.47°C drop, 0.62°C drop, 0.19°C rise, respectively, occurring over 3–6 months. The slow decline in mean temperature during the Development Phase is caused by drop in max temperature and not min temperature. From Peak to Decline, the average change in max, mean, and min temperature is: 0.57°C drop, 0.58°C drop, and 0.63°C drop, respectively, occurring over 1–2 months. At Decline all three temperature components begin to fall,

TABLE 2
Weather conditions at seasonal transmission change-points are compared between disease incidence quartiles

Change-point	Weather component	Q2-Q1		Q3-Q2		Q4-Q3	
		Mean difference	P value	Mean difference	P value	Mean difference	P value
Onset	max temp	0.84	< 0.00001*	0.53	< 0.00001*	0.28	0.0215
	mean temp	0.39	< 0.00001*	0.29	0.0008*	-0.18	0.0564
	min temp	-0.05	0.6102	0.03	0.7451	-0.65	< 0.00001*
	max hum	-2.35	< 0.00001*	-0.90	0.0028*	-1.66	< 0.00001*
	mean hum	-3.93	< 0.00001*	-1.84	0.0002*	-3.34	< 0.00001*
	min hum	-5.20	< 0.00001*	-2.58	< 0.00001*	-4.76	< 0.00001*
	rain	-47.60	< 0.00001*	-28.19	0.0004*	-36.88	< 0.00001*
Peak	max temp	0.01	0.8910	0.09	0.2489	0.36	< 0.00001*
	mean temp	0.07	0.2257	0.11	0.0348	0.24	< 0.00001*
	min temp	0.13	0.0191	0.12	0.0191	0.16	0.0014*
	max hum	-0.21	0.3351	-0.37	0.0418	-0.88	< 0.00001*
	mean hum	-0.14	0.6651	-0.57	0.0269	-1.18	< 0.00001*
	min hum	-0.08	0.8492	-0.46	0.1551	-1.74	< 0.00001*
	rain	3.18	0.6544	-20.26	0.0085	-19.09	0.0008*
Decline	max temp	-0.07	0.5053	0.16	0.0562	0.48	< 0.00001*
	mean temp	0.06	0.5310	0.12	0.1446	0.44	< 0.00001*
	min temp	0.10	0.4379	0.13	0.2419	0.43	< 0.00001*
	max hum	0.11	0.7265	0.52	0.0394	-0.73	0.0003*
	mean hum	0.26	0.5491	0.38	0.3136	-0.83	0.0045*
	min hum	0.27	0.6257	0.43	0.3803	-1.06	0.0078*
	rain	15.73	0.2193	-11.64	0.5702	-10.41	0.4369

*Significant difference detected when $P \leq 0.0125$. P value is adjusted for group-wise multiple comparisons.

particularly min temperature, and thus mean temperature decline accelerates. This change in temperature dynamics is likely responsible for cessation of the Development Phase and earlier Peaks when transmission is highest. These small yet critical changes exemplify how sensitive vector-based dynamics are to slight temperature changes during conditions at Peak. Local timing of these dynamics at the transition from Peak to Decline is responsible for the time lag in epidemic cycles across Thailand. The duality of temperature-humidity drop during Decline Phase regulates the rate of decrease in incidence. Zone 1 temperature falls rapidly, producing a steeper incidence drop than other zones.

Relationship between weather and DENV transmission.

Optimal weather conditions for supporting high levels of transmission are evidenced by the data. Dengue cases occur year round in all zones, but highest incidence rates occur close to Peak in a specific area of the temperature-humidity weather-space. From 1983 to 2001, 1.2 million DHF cases were reported in Thailand. Despite broad seasonal temperature and humidity ranges across provinces, 80% of DHF cases

occurred within 27–29.5°C, 23.5–26.5°C, and 31–35°C mean, min, and max temperature, respectively, and 90% of DHF cases occurred within 26.5–30.5°C, 22.5–26.5°C, and 31–36.5°C mean, min, and max temperature. Within this optimal temperature range, 80% of cases occur above 75%, 55%, and 88% mean, min, and max humidity.

The focus of dengue incidence in a limited weather range is illustrated in Figure 7 for each of the nine geographic zones. Mean incidence rate observed in each weather increment (right column of Figure 7) indicates increased incidence as humidity rises however highest humidity levels are rare events. Distribution of incidence rates in weather-space (center column) reflects the combination of mean incidence rate per weather increment and frequency of occurrence. Thus, highest levels of humidity within each zone do not dominate the distribution of disease but are an important indicator of dynamics. In contrast, as temperature rises to highest levels, mean incidence drops off. Highest observed temperatures are not associated with highest incidence rates. This is likely because highest temperatures often occur when humidity is

TABLE 3
Range of mean weather conditions at change-points across all zones by incidence quartile

	Onset				Peak		Decline	
	Q1	Q2	Q3	Q4	Q1-Q3	Q4	Q1-Q3	Q4
Temp°C								
Max	32.1–34.0	32.7–34.8	32.9–35.6	33.0–35.8	31.7–33.1	32.1–33.4	31.2–32.5	31.6–33.1
Mean	27.4–28.8	27.9–29.0	27.9–29.3	27.6–29.3	27.1–28.4	27.5–28.7	26.5–27.8	26.9–28.3
Min	23.6–25.1	23.7–25.7	23.7–25.7	22.2–25.3	23.5–25.3	23.7–25.7	22.8–24.7	23.6–25.2
Hum%								
Max	88.6–95.3	86.3–94.5	85.0–94.5	84.0–93.7	90.0–95.5*	90.0–94.1*	91.4–95.8§	91.2–94.5§
Mean	74.9–83.9	71.3–81.8	66.9–81.5	63.9–79.1	76.9–84.4†	76.8–82.9†	79.0–85.7¶	78.5–84.2¶
Min	56.9–67.2	50.9–65.2	45.4–62.8	41.0–60.3	58.3–66.9	58.3–66.9	59.2–69.6	60.2–69.2

*Excludes zone 7 range: 87.2–88.6 in Q1–3, 85.0 in Q4

†Excludes zone 7 range: 76.2–77.6 in Q1–3, 74.0 in Q4

§Excludes zone 5,7 range: 85.1–89.3 in Q1–3, 87.9–88.1 in Q4.

¶Excludes zone 5,7 range: 70.1.2–77.2 in Q1–3, 72.9–77.0 in Q4.

||Excludes zone 5 range: 52.2–56.6 in Q1–3, 53.9 in Q4.

TABLE 4
Change in weather conditions at time of seasonal transmission change-points per incidence quartile

Comparison	Weather measure	Q1		Q2		Q3		Q4	
		Mean difference	P value	Mean difference	P value	Mean difference	P value	Mean difference	P value
onset - pre-onset	max temp	-1.64	< 0.00001*	-0.67	< 0.00001*	0.41	0.0112	1.74	< 0.00001*
	mean temp	-0.34	0.0031*	0.28	0.0254	1.32	< 0.00001*	2.30	< 0.00001*
	min temp	1.01	< 0.00001*	1.34	< 0.00001*	2.38	< 0.00001*	2.96	< 0.00001*
	max hum	4.27	< 0.00001*	2.71	< 0.00001*	2.03	< 0.00001*	-0.23	0.43
	mean hum	8.75	< 0.00001*	6.09	< 0.00001*	5.00	< 0.00001*	1.20	0.0018*
	min hum	1.01	< 0.00001*	1.34	< 0.00001*	2.38	< 0.00001*	2.96	< 0.00001*
	rainfall	90.13	< 0.00001*	79.92	< 0.00001*	75.99	< 0.00001*	51.22	< 0.00001*
decline - peak	max temp	-0.62	< 0.00001*	-0.68	< 0.00001*	-0.58	< 0.00001*	-0.47	< 0.00001*
	mean temp	-0.66	< 0.00001*	-0.70	< 0.00001*	-0.66	< 0.00001*	-0.45	< 0.00001*
	min temp	-0.70	< 0.00001*	-0.81	< 0.00001*	-0.76	< 0.00001*	-0.45	< 0.00001*
	max hum	-0.33	0.1724	-0.49	0.0253	0.43	0.0167	0.60	0.0006*
	mean hum	-0.36	0.2939	-0.63	0.0361	0.39	0.1248	0.80	0.0007*
	min hum	-0.58	0.1416	-0.96	0.0084	0.03	0.9339	0.76	0.0094
	rainfall	-9.71	0.2828	6.72	0.4483	11.34	0.1034	21.98	0.0003*

*Significant difference detected when $P \leq 0.00625$. P value is adjusted for group-wise multiple comparisons.

low and negative effects of high temperature on pre-adult vector life stages may limit adult abundance.^{17,21,26–31}

Optimal temperature or optimal humidity alone does not appear to be sufficient to support high rates of transmission. In Figure 8, we illustrate the distribution of Development Phase and Decline Phase province-months in mean

temperature-humidity weather-space for three zones in northwest, eastern, and southern Thailand. In all zones, highest incidence is seen when both temperature and humidity are optimal. In Figure 9, we grid each seasonal change-point in mean temperature-humidity weather-space for all of Thailand during 1983–2001. Nadir is highly dispersed;

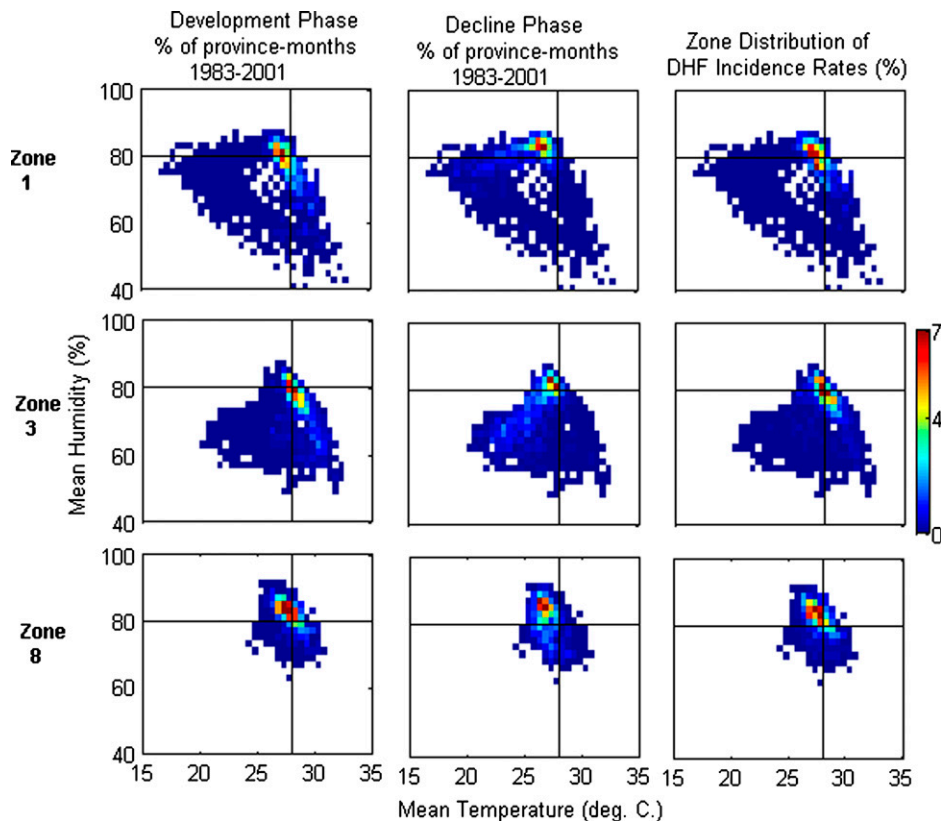


FIGURE 8. Development and Decline Phase in mean humidity-temperature weather-space for three zones of Thailand. Frequency of occurrence of province-months in weather-space during Development Phase and Decline Phase is shown for three zones of contrasting weather patterns for 1983–2001. (Spatial designation of zones is shown in Figure 4; zone 1: northwest, zone 3: central eastern, zone 8: south.) Left column indicates distribution of occurrence of province-months during Development Phase for each of three zones. Center column indicates distribution of occurrence of province-months during Decline Phase. Right column indicates distribution of incidence rates per 100 K population per province-month (% of sum over all weather-space). Grid resolution is 0.5°C, 2% humidity. Reference lines are at 28°C mean temperature and 80% mean humidity. Minimum humidity-temperature and maximum humidity-temperature profiles are provided in the Supplemental Information Figures.

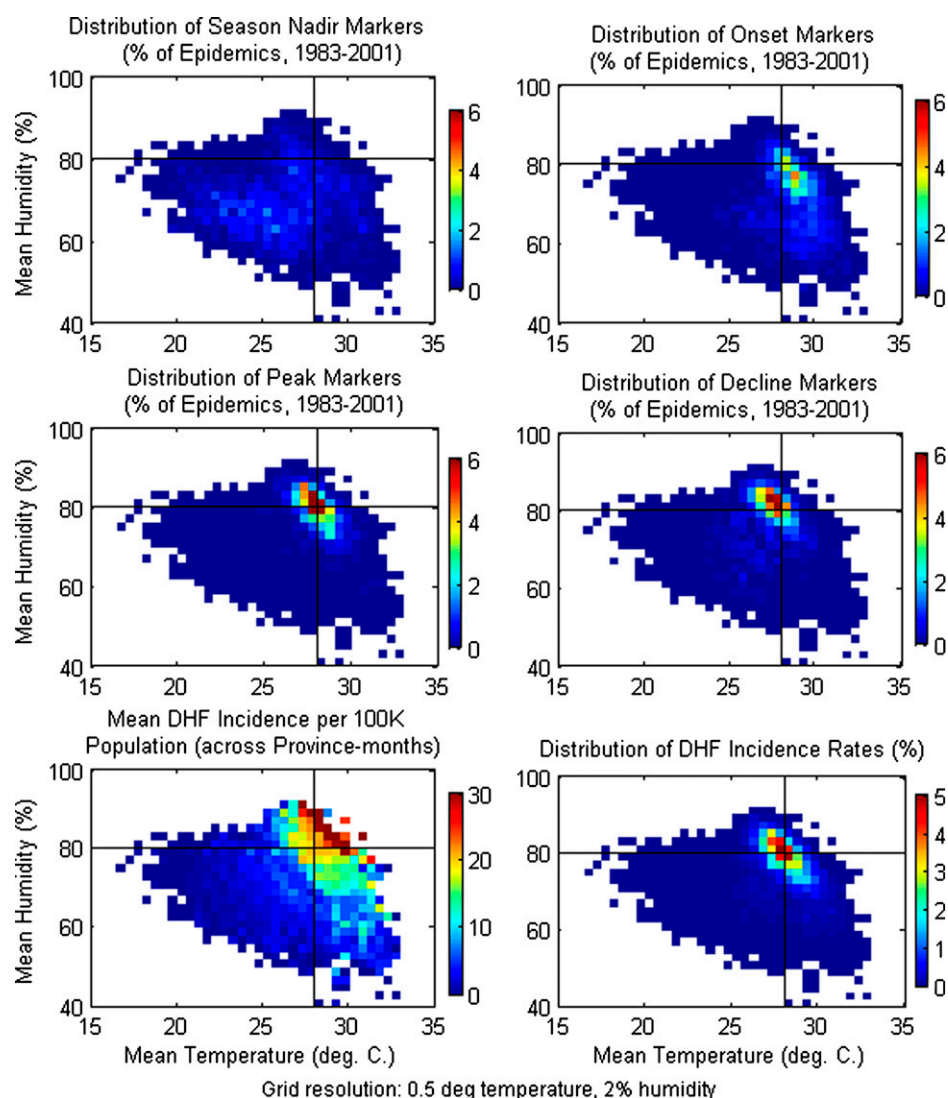


FIGURE 9. Distribution of seasonal transmission change-points in mean humidity-temperature weather-space in Thailand. Distribution of occurrence of change-point markers for all of Thailand in *mean* humidity versus *mean* temperature weather-space, 1983–2001: top left – Nadir, top right – Onset, center left – Peak, center right – Decline. Color indicates percent of total seasonal cycles. Mean dengue hemorrhagic fever (DHF) incidence rate per 100 K population per province-month for each grid interval across weather-space for all Thailand is shown in bottom left panel. Distribution of incidence rates per 100 K population per province-month (% of sum over all weather-space) is shown in bottom right panel. Reference lines are at 28°C mean temperature and 80% mean humidity. Minimum humidity-temperature and maximum humidity-temperature profiles are provided in the Supplemental Figures.

Onset is shifted into higher temperatures; Peak is clustered into a limited temperature-humidity range; and Decline is shifted to slightly lower temperatures and beginning to disperse again. The focal nature of the distribution of all DHF incidence in weather-space in the lower right panel of Figure 9 is a compelling illustration of the regulatory role of weather. (See Figures S1–S4 in the Supplemental Information, for min and max temperature and humidity complements of Figures 8 and 9.)

To predict risk, it is important to understand the variation in these dynamics across seasonal incidence quartiles. In Figure 10, we profile each weather component by change-point and incidence quartile. The most informative difference between quartiles occurs at Onset. Larger epidemics begin earlier during a period of weaker support from humidity but not temperature. Largest epidemics peak slightly earlier at slightly higher temperatures and lower humidity. Develop-

ment rate (the rate of increase in cases) is mapped in weather-space by incidence quartile in Figure 11 and varies significantly from quartile to quartile, particularly *before* optimal temperature-humidity is attained. We performed a Monte Carlo simulation to determine if higher quartile epidemics were associated with a difference in temperature or humidity compared with the same province-month in lower quartile years. Significant effects ($P < 0.05$) were found that suggest year-to-year weather fluctuations play an important but limited role in the quartile class of seasonal cycles (see Methods in the Supplemental Information and Supplemental Table 1). Higher incidence quartile seasons exhibited slightly higher temperature and lower humidity when significant differences were found. These limited effects were focused in mid-late Development Phase (approaching Peak), but not a likely cause of differences in timing of Onset across quartiles. Year-to-year temperature and humidity fluctuations likely contribute to the

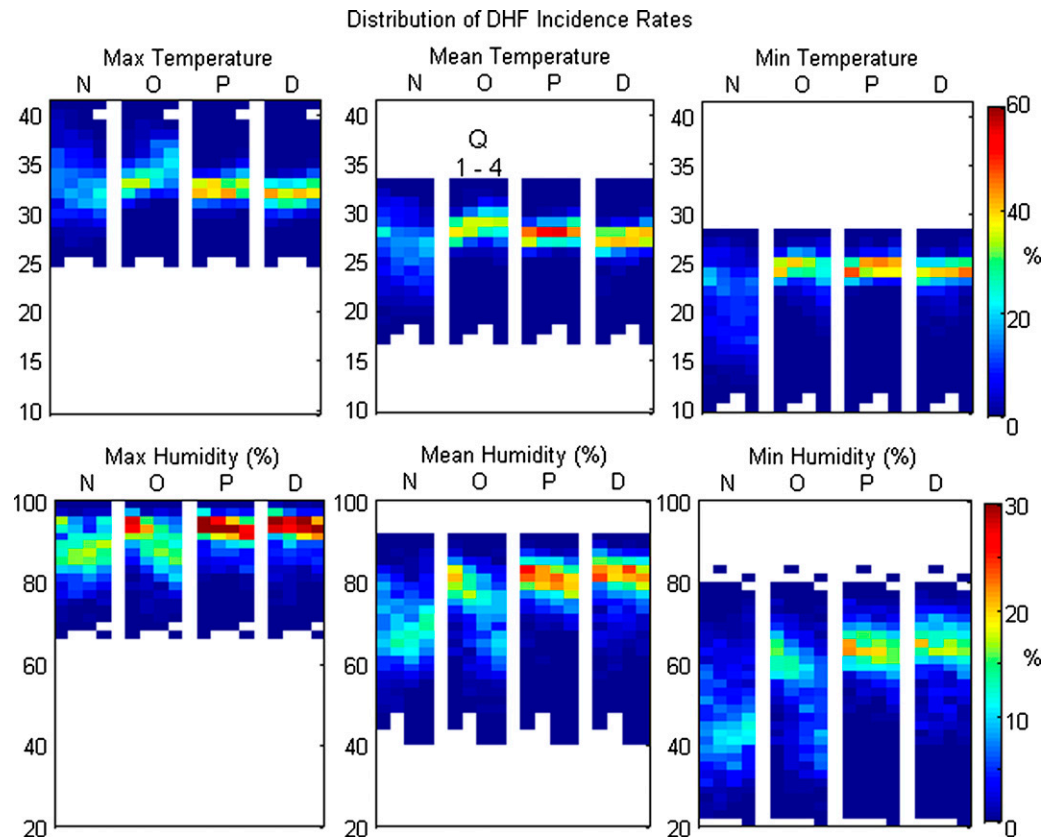


FIGURE 10. Distribution of 1983–2001 dengue hemorrhagic fever (DHF) incidence rates by seasonal transmission change-point and incidence quartile for all of Thailand. Distribution of DHF incidence rates (per 100 K population per province-month) by temperature and humidity weather components for each seasonal transmission change-point marker (N = Nadir, O = Onset, P = Peak, D = Decline) separated by incidence quartiles Q1–Q4 for all of Thailand. Grid resolution is 1°C temperature, 2% humidity.

incidence magnitude of seasonal cycles, but are not the primary driving factor.

Combined effects of temperature and humidity serve as a fundamental regulator of DENV transmission and the structure of seasonal transmission cycles. Transmission potential is linked to specific max, mean, and min temperature windows with the greatest sensitivity associated with mean temperature, but with specific roles of max and min temperature in the timing of transmission change-points. Humidity amplifies the regulation provided by temperature with varying sensitivity at different humidity levels. DHF incidence is negligible below 80% max humidity, 55% mean humidity, and 30% min humidity. DHF incidence is maximized above 88% max humidity, 75% mean humidity and 55% min humidity. The duality of temperature and humidity and its effects on incidence in Thailand is outlined in Figure 12. The regulating effects of temperature are amplified to support higher incidence rates in higher levels of humidity. Highest humidity conditions extend the temperature window in which transmission is likely to occur.

DISCUSSION

The seven components of weather that we examined are highly inter-connected. It is difficult to tease their respective roles apart in relation to virus transmission because a change in one measure directly affects other measures. Despite this complication, important distinctions can be made. We drew

the following conclusions with respect to our five investigative questions.

- (1) Seasonal transmission cycle change-points and phases were effective in characterizing the structure of seasonal transmission cycles, isolating systematic differences across incidence quartiles, and assessing the role of weather in this structure. Higher quartile cycles have earlier Onset and Peak, increased cases at Nadir and Onset, higher DRs, and longer duration of the Development Phase. These characteristics vary geographically across weather zones thus locally measured variations rather than globally standardized thresholds are most informative. Significant variations in dynamics are measurable at Onset and highly predictive of a transmission season before it unfolds.
- (2) The structure of seasonal cycles is regulated by weather. Seasonal change-points in DENV transmission map to change-points in weather dynamics and are highly sensitive to small temperature and humidity variations. Nadir marks the local low in temperature and humidity. Onset marks the transition to transmission-critical mean/min temperature and the beginning of humidity rise associated with the cessation of max temperature rise and onset of the rainy season. Peak marks the fall of mean and min temperature. Decline marks the fall of humidity amidst the fall of temperature.
- (3) The weather range that was optimal for transmission, i.e., when we observed highest incidence, is 28–30°C mean

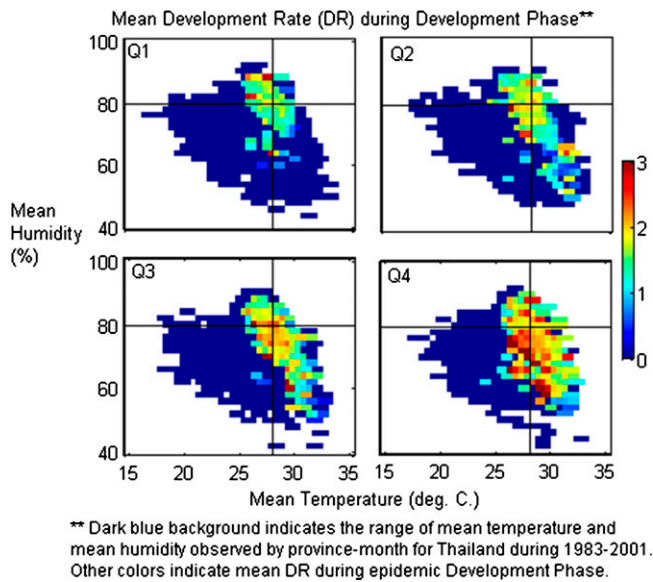


FIGURE 11. Distribution of mean seasonal transmission Development Rate by incidence quartile. Distribution of mean Development Rate during Development Phase per seasonal transmission cycle for all of Thailand is shown in mean humidity-temperature weather-space, 1983–2001: top left – incidence Quartile 1, top right – incidence Quartile 2, bottom left – incidence Quartile 3, bottom right – incidence Quartile 4. Grid resolution is 0.5°C mean temperature, 2% mean humidity. Reference lines are at 28°C mean temperature and 80% mean humidity.

temperature when mean humidity is above 80% and $24.5\text{--}26.5^{\circ}\text{C}$ min temperature when min humidity is above 62%. Max temperature was near 32.5°C and max humidity was above 92% during the highest transmission. Mean temperature appears to have a powerful regulatory role in turning transmission on and off, with a key threshold at 28°C and strong sensitivity to sub-degree

downward increments that directly impact the level of transmission and timing of Peak. This effect may be linked to temperature-sensitive duration of EIP in *Ae. aegypti*, which is critical for transmission.²⁴ Highest mean temperatures were associated with low incidence, which may be linked to the negative effects of temperature extremes on adult survival, larval development, and vector competence.^{30,40–43} Incidence was linked with a min temperature threshold of 24.5°C , but with greater variance with respect to change-points and thus slightly less sensitivity. This may be influenced by pre-adult mosquito life stage development impacting adult abundance and temperature-sensitive vector competence.^{21,25,29}

Our results indicate that temperature defines a viable range for transmission and humidity amplifies the potential within that range. Higher humidity and lower temperature benefit vector survival and may enhance probability of transmission through increased adult abundance and duration of post-EIP survival.²⁷ Higher humidity in conjunction with optimal temperature may increase vector competence.³⁵ Effects of humidity in combination with the influence of temperature on pre-adult development, adult survival, length of EIP, and vector competence are viable explanations for high transmission rates observed when temperature and humidity are optimal, but lacking when one of these components is not supported.

Rainfall is critically important, but does not systematically amplify transmission. The critical rise in humidity is associated with start of the rainy season. Earliest Onsets occur just after the rainy season begins. Incidence increases as humidity rises. In Thailand, 77% of *Ae. aegypti* may reside indoors and use aquatic larval development sites in or near the home.^{17,22} If 23% of larval development sites are outdoors, start of the rainy season may boost population development by providing needed water in desiccated containers. Each of these factors contributes separate probabilities to the overall probability of transmission as

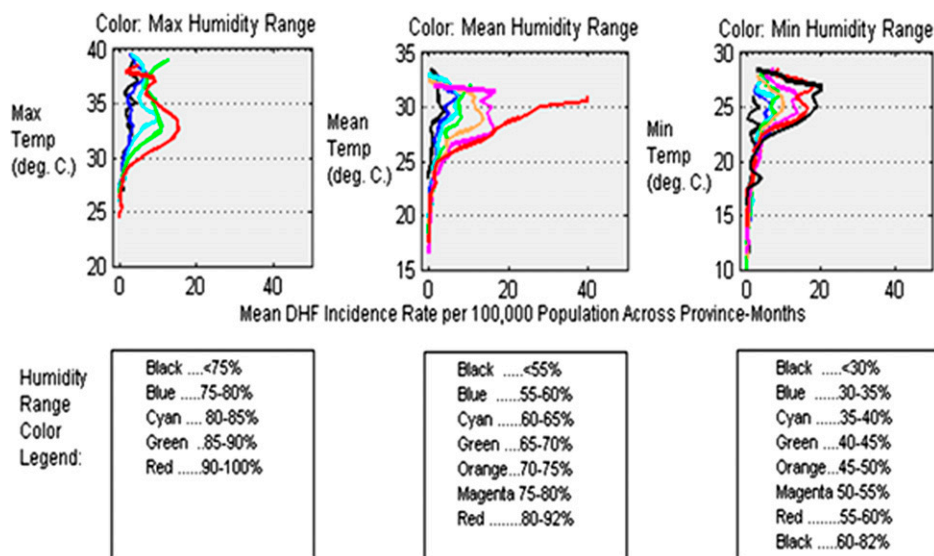


FIGURE 12. Combined effects of temperature and humidity on dengue hemorrhagic fever (DHF) incidence rates for all Thailand provinces, 1983–2001. The DHF incidence rate per 100 K population per province-month is averaged in 0.5°C temperature increments for different intervals of relative humidity (%) indicated by colors. Left: Maximum humidity and maximum temperature, center: mean humidity and mean temperature, right: minimum humidity and minimum temperature.

described in Figure 1. Interaction between temperature and humidity is tightly linked. Weaker support from one component is compensated to some degree by enhancements from the other. The duality of temperature and humidity is central to transmission.

No cases were reported when mean temperature was below 21°C or min temperature was below 14.5°C. This is consistent with field and laboratory studies that report failure to obtain virus from salivary glands when mosquitoes are maintained at 20°C and failure for larvae to reach adult stage below 14°C. These temperatures may represent a weather barrier for sustained transmission.^{29–31}

- (4) Year-to-year fluctuations in weather, specifically slightly higher temperature and lower humidity in the mid and late Development Phase, are associated with higher quartile transmission cycles but do not fully explain higher levels of transmission. We expect the driving factor that distinguishes Q4 epidemics from Q1 seasonal cycles is not related to weather, but rather to susceptibility in the local human population for specific serotype(s) in circulation at the time. In an endemic setting, the probability of human susceptibility to a potential infection can vary considerably in space and time and serve as a significant multiplier in the overall probability of transmission. This factor can act as a catalyst to amplify the probability of transmission where the total probability from weather-induced factors is weak. Even a slight amplification that produces early Onset or a few more early cases can have a major impact by the time Peak is reached. The weakest seasonal cycles, Q1, have the latest onset when support from weather is optimal and near Peak. It makes sense that this would be the case if the probability of transmission in Q1 seasonal cycles draws little support from susceptibility in the human population.
- (5) The Quiet Phase is critically important. Although case counts are low, this is the time when epidemic transmission is staged. By Onset, there is sufficient data to predict the course of an epidemic. Onset that is 2 weeks earlier or has a few more cases can raise the quartile class of a developing epidemic by the time it reaches Peak. The Quiet Phase should be carefully monitored to target interventions pre-emptively when small changes can produce large benefits in prevention. Interventions should be applied early. In a Development Phase where case counts double for eight generations, 20 cases at Onset becomes 20 > 40 > 80 > 160 > 320 > 640 > 1,280 > 2,560 > 5,120, a total of 10,220 cases. 87.5% of cases occur in the last three generations. Such a disease course could be substantially reduced if Onset is immediately recognized and intervention is administered early. The Quiet Phase may be the most important period to monitor to effectively prioritize and target interventions in a pre-emptive strategy.

This study focuses on the relationship between local weather dynamics and critical change-points in seasonal dengue transmission cycles. Systematic comparisons between seasonal cycles of different incidence magnitude have provided new insights regarding the fundamental link between weather, vector dynamics, and the probability of virus transmission. The probability of a single transmission event is driven by a complex combination of many different factors associated with human, vector, and pathogen dynamics. An

enhanced understanding of the role of weather in regulating seasonal cycles provides needed tools for improved development of human-vector virus transmission models, a more informative dynamic estimation of risk and early prediction of large epidemics, and more effective preemptive intervention planning and use of prevention resources.

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